REMARKS

Applicants have amended the title to more specifically describe the invention. Submitted herewith is a response to the Notice to Comply, which amends the specification to include a copy of the sequence listing.

Applicants have cancelled Claim 15 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Applicants have amended Claims 1-12, and 14 to remove reference to the Figures. Claims 1-6, 9-10 and 14 have been amended to specify the extracellular domains. Claims 1-5 have been amended to add the limitation that the claimed nucleic acids are more highly expressed in esophageal tumor tissue, lung tumor tissue, normal kidney tissue, or normal skin tissue compared to normal esophageal tissue, normal lung tissue, kidney tumor tissue or melanoma tumor tissue, respectively, or encodes a polypeptide that is more highly expressed in esophageal tumor tissue, lung tumor tissue, normal kidney tissue, or normal skin tissue compared to normal esophageal tissue, normal lung tissue, kidney tumor tissue or melanoma tumor tissue, respectively. Claim 14 has been amended to specify the conditions under which hybridization occurs. Applicants maintain that the amendments add no new matter and are fully supported by the specification as originally filed. For example, support for the amendments to Claims 1-6, 9-10 and 14 specifying the extracellular domain can be found in Figure 120, for example. Support for the amendments to Claims 1-5 can be found in Example 18 beginning at paragraph [0529], as well as paragraph [0336] of the specification. Support for the amendment to Claim 14 can be found in the definition of stringent conditions in paragraph [0227] of the specification.

Claims 1-14, and 16-20 are presented for examination. Applicants respond below to the specific rejections raised by the PTO in the Office Action mailed September 21, 2004. For the reasons set forth below, Applicants respectfully traverse.

Correction of Inventorship under 37 CFR §1.48(b)

Applicants request that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. The fee as set forth in § 1.17(i) is submitted herewith.

Appl. No.

: 10/063,732

Filed

May 8, 2002

Specification:

The PTO has objected to the title as not being descriptive. Applicants have amended the title herein.

The PTO has stated that the application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). The PTO states that the application fails to comply with the requirements of 37 C.F.R. § 1.821 through 1.825 because the application does not contain, as a separate part of the disclosure on a paper copy, a Sequence Listing as required by 37 C.F.R. § 1.821(c).

Applicants submit herewith a response to the Notice to Comply which amends the specification to include a paper copy of the Sequence Listing, which is also submitted herewith.

IDS:

The PTO has requested additional information on the references cited in the BLAST results reported in the Information Disclosure Statement filed September 17, 2002. Applicants submit herewith more detailed information regarding the publication date of the cited sequences (attached as Exhibit 1).

Priority Determination:

The PTO has stated that because the claimed nucleotide has no utility, the priority under 35 U.S.C. § 120 is set at the instant filing date, May 8, 2002. Applicants have previously listed the priority information for the instant application in a Preliminary Amendment mailed September 5, 2002. The preliminary amendment states that the instant application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, which is a continuation-in-part of, and claims priority under 35 U.S.C. § 120 to, US Application 09/403297 filed 10/18/1999, now abandoned, which is the National Stage filed under 35 U.S.C. § 371 of PCT Application PCT/US99/20111 filed 9/1/1999, which claims priority under 35 U.S.C. § 119 to US Provisional Application 60/105002 filed 10/20/1998.

Applicants submit that for the reasons stated below, the claimed nucleic acids have a credible, substantial, and specific utility. The sequences of SEQ ID NOs: 119 and 120 were first disclosed in US Provisional Application 60/105002 filed 10/20/1998 in Figures 2A-C and 1. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed nucleic acids, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35.

Rejections under 35 U.S.C. § 112, second paragraph – Indefiniteness

The PTO has rejected Claims 1-6, 8-10 and 14-20 under 35 U.S.C. § 112, second paragraph, as being indefinite. The PTO objects to the phrase "the extracellular domain" as PRO1573 is not disclosed as being expressed on a cell surface. The PTO further objects to the recitation of "the extracellular domain", "lacking its associated signal sequence" because a signal sequence is not generally considered part of an extracellular domain.

Applicants respectfully submit that the pending claims are not indefinite as both the extracellular domain and the signal peptide regions are well-defined in the specification. For example, Figure 120 indicates that SEQ ID NO: 120 has three transmembrane domains, and thus two extracellular domains, as well as a signal peptide. However, Applicants have amended Claims 1-6, 9-10, and 14 to specify the extracellular domain. In the interest of advancing prosecution of this application, Applicants will acquiesce to the PTO's assertion that a signal peptide is not normally considered part of the extracellular domain. By making this concession, Applicants understand that element (c) of Claims 1-6 and 14, as well as Claim 9, describes a nucleic acid sequence encoding the extracellular domain of the polypeptide of SEQ ID NO: 120, lacking its associated signal peptide. At the same time, as amended, element (d) of Claims 1-6 and 14, as well as Claim 10, describes a nucleic acid sequence encoding the extracellular domain of the polypeptide of SEQ ID NO: 120, including its associated signal peptide. Applicants state that this argument is made only in connection with the instant application, and does not reflect the Applicants' interpretation of any claims in any related applications.

The PTO also objects to the use of "hybridize" and "stringent conditions" since what hybridizes depends on the conditions under which the hybridization is carried out, and "stringent conditions" is a relative term. Applicants have amended Claims 14 and 16 to specify the

conditions under which the hybridization occurs. Thus, Applicants request that the PTO reconsider and withdraw the indefiniteness rejection under 35 U.S.C. §112, second paragraph.

Rejection under 35 U.S.C. §101 – Utility

The PTO has rejected Claims 1-20 as lacking a specific, substantial, and credible utility. The PTO asserts that there is no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner, or any other specific feature that is disclosed as being associated with PRO1573. One of the asserted utilities for the claimed nucleic acids is use as a diagnostic tool, as well as therapeutically as a target for treatment, based on the data that PRO1573 cDNA is more highly expressed in esophageal tumor tissue, lung tumor tissue, normal kidney tissue, or normal skin tissue compared to normal esophageal tissue, normal lung tissue, kidney tumor tissue or melanoma tumor tissue, respectively.

The PTO has rejected this utility because the specification does not disclose the biological significance of this high or low expression levels, nor the correlation between the high/low expression of the DNA encoding protein PRO1573 and a predisposition to the onset of lung tumor, i.e., whether it is the cause or the result of the tumors. The PTO further argues that there is no supporting evidence to indicate that the polypeptide encoded by the claimed nucleic acids of the instant invention is more highly expressed in some normal tissue compared to their tumor counterparts. The PTO also asserts that the evidence that the polynucleotide is more highly expressed in esophageal tumor, normal kidney, lung tumor and normal skin is insufficient because it does not disclose what the normal level of expression is, does not indicate how high the expression level is compared to for example normal esophagus, kidney tumor, normal lung and melanoma tumor, it lacks statistical correlation, and because the type or kind of tumor, even if it is malignant, is not described. The PTO asserts that without knowing the identity of the tumor, one of skill in the art cannot use the polynucleotides for diagnostic or therapeutic purposes. The PTO concludes that the specification does not disclose a correlation between any specific disorder and the altered level or form of the claimed polypeptides, and does not teach or describe the function of this yet to be identified polypeptide.

The PTO acknowledges that "[t]he polynucleotide may have utility because either its presence or absence or elevation or reduction is correlated to a disease." Office Action at 7. The PTO states that if this is not the case, then a utility for the encoded polypeptide will confer utility

on the polynucleotide. Office Action at 7. The PTO states that there is no supporting evidence to indicate that the polypeptide encoded by the nucleotide of the instant invention is more highly expressed in tumor compared to normal tissue. Finally the PTO argues that there is no necessary correlation between gene copy number, gene expression and protein expression.

Applicants respectfully disagree.

<u>Utility – Legal Standard</u>

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added.)

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

<u>Utility need NOT be Proved to an Absolute Certainty – a Correlation between the Evidence and</u> <u>the Asserted Utility is Sufficient</u>

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." In re Langer, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). See, also In re Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); In re Irons, 340 F.2d 974, 144 USPQ 351 (1965); In re Sichert, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. Raytheon v. Roper, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout ex parte examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

[T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not. M.P.E.P. at § 2107.02, part VII (2004) (emphasis in original, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In Fujikawa v. Wattanasin, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

[T]esting is often required to establish practical utility. But the test results need not absolutely prove that the compound is pharmacologically active. All that is required is that the tests be "reasonably indicative of the desired [pharmacological] response." In other words, there must be a sufficient correlation between the tests and an asserted pharmacological activity so as to

convince those skilled in the art, to a reasonable probability, that the novel compound will exhibit the asserted pharmacological behavior." Fujikawa v. Wattanasin, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a therapeutic and diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

The Court in *Fujikawa* relied in part on its decision in *Cross v. IIzuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

[I]n vitro results...are generally predictive of in vivo test results, i.e., there is a reasonable correlation therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between in vitro test results and in vivo test results. Rather, [Appellee's] position is that successful in vitro testing for a particular pharmacological activity establishes a significant probability that in vivo testing for this particular pharmacological activity will be successful. Cross v. IIzuka, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

The Cross case is very similar to the present case. Like in vitro testing in the pharmaceutical industry, those of skill in the field of biotechnology rely on the reasonable correlation that exists between gene expression and protein expression (see below). Were there no reasonable correlation between the two, the techniques that measure gene levels such as microarray analysis, differential display, and quantitative PCR would not be so widely used by those in the art. As in Cross, Applicants here do not argue that there is "an invariable exact correlation" between gene expression and protein expression. Instead, Applicants' position detailed below is that a measured increase in gene expression in cancer cells establishes a

"significant probability" that the encoded polypeptide will also be overexpressed in cancer based on "a reasonable correlation therebetween".

Taken together, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The standard is not absolute certainty.

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool for cancer.

Substantial Utility

Applicants have established that the Gene Encoding the PRO1573 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue and is Useful as a Diagnostic Tool

Applicants first address the PTO's argument that the evidence of differential expression of the gene encoding the PRO1573 polypeptide in certain tumors compared to their normal counterparts is insufficient because it does not disclose what the normal level of expression is, does not indicate how high the expression level is compared to the normal or tumor counterpart, it lacks statistical correlation, and because the type or kind of tumor, even if it is malignant, is not described. Applicants also address the PTO's argument that because the specification does not disclose the biological significance of these high or low expression levels, nor the correlation between the high/low expression of the DNA encoding protein PRO1573 and a predisposition to the onset of lung tumor, i.e., whether it is the cause or the result of the tumors, the data does not establish a utility. Applicants submit that the gene expression data provided in Example 18 of the present application are sufficient to establish a specific and substantial utility for the claimed nucleic acids related to the gene encoding the PRO1573 polypeptide.

Applicants submit herewith a copy of a declaration of J. Christopher Grimaldi, an expert in the field of cancer biology, originally submitted in a related co-pending and co-owned patent application Serial No. 10/063,557 (attached as Exhibit 2). In paragraphs 6 and 7, Mr. Grimaldi

explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or underexpressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal." He explains that, contrary to the PTO's assertions, "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue. The precise type of tumor is also irrelevant; again, the assay was designed to indicate whether a difference exists between normal tissue and tumor tissue of the same type." (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise type of tumor and level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. Similarly, the biological significance of the high/low expression of the PRO1573 gene is irrelevant, as is whether it is a cause or result of the tumor. Resolution of these issues is not required to use the claimed nucleic acids as tumor diagnostic tools – one does not have to know why the PRO1573 gene is differentially expressed in certain tumors to use it as a tumor marker. As Mr. Grimaldi states, "If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

The PTO also argues that because cancerous tissue can be aneuploid, and the data in the instant application was not corrected for aneuploidy, "a higher amplification of a gene does not necessarily mean higher expression or lower in a tissue, but can merely be an indication that the cancer tissue is aneuploid." Office Action at 8.

Applicants agree that it is possible that the results reported in Example 18 may be due to aneuploidy in the tumor cells tested. However, Applicants fail to see how it is relevant to the utility of the claimed nucleic acids, or their corresponding polypeptides, whether the differential expression reported in Example 18 is due to aneuploidy or not. Regardless of whether the differential expression of the gene encoding PRO1573 is a result of increased or decreased transcription of the gene, aneuploidy, or some other regulatory mechanism, the fact remains that it is more highly expressed in esophageal tumor tissue, lung tumor tissue, normal kidney tissue,

or normal skin tissue compared to normal esophageal tissue, normal lung tissue, kidney tumor tissue or melanoma tumor tissue, respectively, and it is therefore useful as a diagnostic tool for cancer since it can be used as a molecular marker for cancer.

Applicants have established that the Accepted Understanding in the Art is that there is a Direct Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

The PTO acknowledges that if the PRO1573 protein has utility, then this confers utility on the polynucleotide encoding the protein. Office Action at 7. However, the PTO argues that there is no supporting evidence that the polypeptide encoded by the polynucleotide of the instant invention is more highly expressed in esophageal tumor tissue, lung tumor tissue, normal kidney tissue, or normal skin tissue compared to normal esophageal tissue, normal lung tissue, kidney tumor tissue or melanoma tumor tissue, respectively. The PTO argues that cancerous tissue is known to be aneuploid, and that higher amplification of a gene does not necessarily mean higher or lower expression in a tissue, but can merely be an indication that the cancer tissue is aneuploid. The PTO also states that the literature reports that it does not necessarily follow that an increase in gene copy number results in increased gene expression and increased polypeptide expression. Relying on Pennica et al., 1998, PNAS USA 95:14717-14722 (hereinafter Pennica), the PTO states that one cannot extrapolate the expression data provided in the specification to support the implicit assertion that the polynucleotides encoding PRO1573 can be used in cancer diagnosis or therapy.

Applicants submit that those of skill in the art would recognize that amplification of a gene due to aneuploidy will more likely than not lead to an increase in expression of that gene as measured by the level of mRNA. This assertion is supported by numerous references. Orntoft et al. (Molecular and Cellular Proteomics, 1:37-45 (2002)) (submitted herewith as Exhibit 3) studied transcript levels of 5600 genes in malignant bladder cancers which were linked to a gain/loss of chromosomal material using an array-based method. Orntoft et al. showed that there was a gene dosage effect and teach that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (Orntoft at 37, column 1, abstract). In addition, Hyman et al. (Cancer Research, 62:6240-6245 (2002)) (submitted herewith as Exhibit 4) used CGH analysis and cDNA microarrays to compare DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines.

They showed that there is "evidence of a prominent global influence of copy number changes on gene expression levels" (Hyman at 6244, column 1, last paragraph).

Additional supportive teachings are also provided by Pollack *et al.* (*PNAS*, 99:12963-12968 (2002)) (submitted herewith as Exhibit 5) who studied a series of primary human breast tumors and found that "[b]y analyzing mRNA levels in parallel, we have also discovered that *changes in DNA copy number have a large, pervasive, direct effect on global gene expression patterns* in both breast cancer cell lines and tumors." (Pollack at 12967 at column 1, emphasis added). Their study found that "62% of highly amplified genes show moderately or highly elevated expression, that DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels." (Pollack at 12963, column 1, abstract). This report is particularly persuasive because the high-resolution comparative genomic hybridization analysis used to assess DNA copy number was particularly sensitive.

Together, these articles collectively teach that in general, gene amplification increases mRNA expression. As discussed below, it is also the established general rule in the art that the level of protein expression is directly related to the level of gene expression, so that increased gene expression leads to increased protein expression.

Relying on a single example of one gene, the PTO states that the literature reports that it does not *necessarily* follow that an increase in gene copy number results in increased gene expression and increased polypeptide expression. The PTO focuses on the statement from Pennica that the *WISP-2* gene <u>DNA was amplified</u> in colon tumors, but its <u>mRNA expression</u> was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient. Office Action at 8-9. As an aside, it should be noted that this result may not even be real, as the authors explain: "Because the center of the 20q13 amplicon [of which *WISP-2* is a part] has not yet been identified, it is possible that the <u>apparent amplification</u> observed for *WISP-2* may be caused by another gene in this amplicon." Pennica at 14722 (emphasis added).

However, even if the lack of correlation between DNA copy number and mRNA level in Pennica is real, Pennica says nothing about a lack of correlation between the level of mRNA and the level of protein expression – Pennica did not even look at protein expression. It is the

correlation between mRNA level, as assessed by probing the cDNA library, and the level of protein expression which is at issue here, not the correlation of gene copy number and mRNA levels. The data Applicants report in Example 18 indicate that there are more copies of the mRNA encoding PRO1573 in esophageal tumor tissue, lung tumor tissue, normal kidney tissue, or normal skin tissue compared to normal esophageal tissue, normal lung tissue, kidney tumor tissue or melanoma tumor tissue, respectively. Nothing in Pennica is contrary to Applicants' assertion that it is well-established in the art that the level of protein is positively correlated to the level of mRNA. Applicants respectfully submit that by relying on Pennica, the PTO is confusing the relationship between an increase in copy number of a gene or gene amplification on the one hand, and increased expression of a gene or mRNA expression on the other.

As stated above, the standard for establishing a use for a claimed invention is not absolute certainty, and thus a *necessary* correlation between mRNA levels and protein levels is not required.

[T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not. M.P.E.P. at § 2107.02, part VII (2004) (emphasis in original, internal citations omitted).

Even if Pennica supported the PTO's argument, which it does not, one contrary example does not establish that one of skill in the art would find it is more likely than not, that in general, there is no correlation between <u>mRNA</u> level and <u>protein</u> levels. In fact, the working hypothesis among those skilled in the art is that there is a direct correlation between mRNA levels and protein levels.

Applicants submit herewith a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology (attached as Exhibit 6). This declaration was submitted in connection with the related co-pending and co-owned application Serial No. 10/063,557. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased

polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also submit herewith a copy of the declaration of Paul Polakis, Ph.D. (attached as Exhibit 7), an expert in the field of cancer biology, originally submitted in a related and co-owned patent application Serial No. 10/032,996. As stated in paragraph 6 of his declaration:

Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein. (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (4th ed. 2002) submitted herewith as Exhibit 8). Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Molecular Biology of the Cell at 302, emphasis added. Similarly, figure 6-90 on page 364 illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Molecular Biology of the Cell at 364. This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Molecular Biology of the Cell at 379.

Together, the declarations of Grimaldi and Polakis, the accompanying references, and the excerpts from the Molecular Biology of the Cell all establish that the accepted understanding in the art is that there is a reasonable correlation between gene expression and the level of the encoded protein. In light of the lack of support for any argument by the PTO to the contrary, Applicants submit that they have established that it is more likely than not that one of skill in the art would believe that because the PRO1573 mRNA is differentially expressed in esophageal, lung, kidney and skin tumors compared to their normal tissue counterparts, the PRO1573 polypeptide will also be differentially expressed in esophageal, lung, kidney and skin tumors compared to their normal tissue counterparts. One of skill in the art would recognize that a protein which is differentially expressed in certain cancer cells compared to the corresponding normal tissue would have utility as a diagnostic tool. As the PTO has acknowledged, "if the protein has utility, then this confers utility upon the polynucleotide...." Thus, Applicants submit that they have established that it is more likely than not that one of skill in the art would recognize the asserted utility of the PRO1573 polypeptide, and the nucleic acids which encode it, as a cancer diagnostic tool.

Applicants submit that they have therefore established two separate basis for utility of the claimed nucleic acids. The first argument is based on the higher expression of the PRO1573 gene in esophageal tumor tissue, lung tumor tissue, normal kidney tissue, or normal skin tissue compared to normal esophageal tissue, normal lung tissue, kidney tumor tissue or melanoma tumor tissue, respectively. The second argument is based on the utility of the PRO1573 polypeptides as diagnostic tools, given that it is well-established in the art that there is a correlation between gene expression and protein expression. As the PTO acknowledges, the utility of the polypeptide confers utility on the encoding gene as well.

The Claimed Nucleic Acids would have Diagnostic Utility even if there is no Direct Correlation between Gene Expression and Protein Expression

Even assuming *arguendo* that, there is no direct correlation between gene expression and protein expression for PRO1573, which Applicants submit is not true, a polypeptide encoded by a gene that is differentially expressed in cancer would **still** have a credible, specific and substantial utility.

In paragraph 6 of the Grimaldi Declaration, Exhibit 6, Mr. Grimaldi explains that:

However, even in the rare case where the protein expression does not correlate with the mRNA expression, this still provides significant information useful for cancer diagnosis and treatment. For example, if over- or under-expression of a gene product does not correlate with over- or under-expression of mRNA in certain tumor types but does so in others, then identification of both gene expression and protein expression enables more accurate tumor classification and hence better determination of suitable therapy.

This conclusion is echoed in the Declaration of Avi Ashkenazi, Ph.D. (attached as Exhibit 9), an expert in the field of cancer biology. This declaration was previously submitted in connection with co-pending application Serial No. 09/903,925. Applicants submit that simultaneous testing of gene expression and gene product expression enables more accurate tumor classification, even if there is no positive correlation between the two. This leads to better determination of a suitable therapy.

This is further supported by the teachings in the article by Hanna and Mornin (attached as Exhibit 10). The article teaches that the HER-2/neu gene has been shown to be amplified and/or overexpressed in 10%-30% of invasive breast cancers and in 40-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the overexpression of the HER-2/neu gene product (by IHC). Even when the protein is not overexpressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The Applicants have established that it is the general, accepted understanding in the art that there is a positive correlation between gene expression and protein expression. However, even when this is not the case, a polypeptide encoded by a gene that is differentially expressed in cancer would still have utility, as would the nucleic acid which encodes it. Thus, Applicants have demonstrated another basis for supporting the asserted utility for the claimed nucleic acids.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Nucleic Acids

Applicants next address the PTO's assertions that there is no biological activity, expression pattern, phenotype, disease of condition, ligand, binding partner, or any other specific feature that is disclosed as being associated with PRO1573. Applicants respectfully disagree.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention."

M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1573 gene in certain types of cancer cells, along with the declarations discussed above, provide a specific utility for the claimed nucleic acids.

As discussed above, there are significant data which show that the gene encoding the PRO1573 polypeptide is more highly expressed in esophageal tumor tissue, lung tumor tissue, normal kidney tissue, or normal skin tissue compared to normal esophageal tissue, normal lung tissue, kidney tumor tissue or melanoma tumor tissue, respectively. These data are strong evidence that the gene encoding the PRO1573 polypeptide is associated with esophageal, lung, kidney and melanoma tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the gene encoding PRO1573 with a specific disease. The asserted utility as a diagnostic tool for cancer, particularly esophageal, lung, and kidney tumor, and melanoma, is a specific utility – it is not a general utility that would apply to the broad class of nucleic acids.

Conclusion

The PTO has asserted two arguments for why there is a lack of a substantial utility: (1) that the data reporting differential expression of the PRO1573 gene in certain cancers is not reliable; and, (2) that because there is no necessary correlation between gene amplification and protein expression, the claimed nucleic acids cannot be used as cancer diagnostic or therapeutic tools. Applicants have addressed each of these arguments in turn.

First, the Applicants provide a declaration stating that the data in Example 18 reporting higher expression of the PRO1573 gene in esophageal tumor tissue, lung tumor tissue, normal kidney tissue, or normal skin tissue compared to normal esophageal tissue, normal lung tissue, kidney tumor tissue or melanoma tumor tissue, respectively, are real and significant. This declaration also indicates that given the relative difference in expression levels, the claimed nucleic acids have utility as cancer diagnostic tools. Applicants have also shown that whether the differential expression of the PRO1573 gene is due to aneuploidy or not does not affect its usefulness as a diagnostic tool.

Next, the Applicants have shown that the reference cited by the PTO to support its conclusion that there is no necessary correlation between the level of gene expression and mRNA or protein expression does not support the PTO's position. Applicants have presented the

declarations of two experts in the field along with supporting references which establish that the general, accepted view of those of skill in the art is that there is a direct correlation between mRNA levels and the encoded protein levels. Thus, one of skill in the art would find that it is more likely than not that the PRO1573 protein has utility as a diagnostic tool for cancer, and as the PTO acknowledges, nucleic acids encoding the polypeptide also have utility as a result.

Applicants have also presented the declarations of two experts in the field, along with supporting references, which establish that even in the anomalous case where there is no positive correlation between gene expression and expression of the encoded protein, the simultaneous monitoring of both is useful for diagnosis and further classification of the cancer.

Finally, the PTO asserts that there is no asserted specific utility because there is no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner, or any other specific feature associated with PRO1573. Applicants have pointed out that the substantial utilities described above are specific to the claimed nucleic acids because the gene encoding PRO1573 is differentially expressed in certain cancer cells compared to the corresponding normal cells. This is not a general utility that would apply to the broad class of nucleic acids.

Thus, given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed nucleic acids as a diagnostic agent. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is <u>not</u> required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed nucleic acids relating to PRO1573 set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejection under 35 U.S.C. §112, first paragraph - Enablement

The PTO rejected Claims 1-20 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to use the invention. The PTO argues that because the claimed invention is not supported by a substantial, specific and credible utility, the claims are not enabled. The PTO also

states that even if a specific and substantial utility were established, they are enabled only for polynucleotides of SEQ ID NO: 119 and fragments that are usable as hybridization probes, they are not enabled for claims to polynucleotides with 80-99% sequence identity to SEQ ID NO: 119, those which encode polypeptides with 80-99% sequence identity to SEQ ID NO: 120, or those which hybridize to any of the above because there is no structural or functional information provided in the specification. The PTO states that there is insufficient guidance regarding how to make PRO1573 polynucleotide variants. The PTO also states that the hybridization claims are not enabled because they do not recite that the polynucleotide encodes a protein having a specifically disclosed activity. The PTO next asserts that even if utility of the claimed nucleic acids as hybridization probes is established, degenerate sequences are not enabled.

As an initial matter, Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed nucleic acids. Applicants therefore request that the PTO reconsider and withdraw the enablement rejection to the extent that it is based on a lack of utility for the claimed nucleic acids.

The PTO asserts that even with an established utility, only polynucleotides of SEQ ID NO: 119 are enabled because there is no structural or functional information provided. Applicants have amended the claims to incorporate the limitation that the claimed nucleic acids with less than 100% identity to SEQ ID NO: 119, or which encode a protein with less than 100% identity to SEQ ID NO: 120, must be more highly expressed in esophageal tumor tissue, lung tumor tissue, normal kidney tissue, or normal skin tissue compared to normal esophageal tissue, normal lung tissue, kidney tumor tissue or melanoma tumor tissue, respectively, or encode a polypeptide that is more highly expressed in esophageal tumor tissue, lung tumor tissue, normal kidney tissue, or normal skin tissue compared to normal esophageal tissue, normal lung tissue, kidney tumor tissue or melanoma tumor tissue, respectively. Applicants assert that techniques used to make variants of polynucleotide or polypeptide sequences are well-known to those of skill in the art (see, e.g., paragraph [0258] of the specification). Thus, the claims as amended contain sufficient structural information to enable the claims.

Applicants respectfully disagree that the hybridization claims are not enabled. First, Applicants assert that those of skill in the art are well aware of which sequences will hybridize under various hybridization conditions. This is especially true as Applicants have amended the

claims to include specific conditions under which the claimed hybridization occurs. Applicants submit that by disclosing the sequence of the target nucleic acid along with the specific hybridization conditions, Applicants have disclosed sufficient structural information about the claimed nucleic acids such that those of skill in the art would know how to make them. Second, Applicants submit that undue experimentation would not be required to use the claimed nucleic acids as diagnostic tools. The level of skill in the art is high, and methods of using nucleic acid sequences as probes are well-known and well-established in the art. One of skill in the art would know how to use the claimed nucleic acids, for example, as hybridization probes for the diagnosis of cancer as outlined in the specification at, for example, paragraph [0336], and Example 18 beginning at paragraph [0529].

Finally, Applicants note that because they have established a utility for the PRO1573 polypeptide, supported by the declarations of experts in the field and several references, polynucleotides which encode the PRO1573 polypeptide also have utility. This includes degenerate polynucleotide sequences which encode the PRO1573 polypeptide. Therefore, contrary to the PTO's assertion, polynucleotides that differ from SEQ ID NO: 119 due to codon degeneracy are enabled.

In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §112, first paragraph – Written Description

The PTO has rejection of Claims 1-5 and 15-20 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the invention. According to the PTO, because the claims do not require that the claimed polynucleotides encode a particular protein, or that any encoded protein possess any particular biological activity, the claims fail the written description requirement.

The Legal Standard for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is whether the disclosure "reasonably conveys to artisan that the inventor had possession at that time of the later claimed subject matter." In re

Kaslow, 707 F.2d 1366, 1375, 2121 USPQ 1089, 1096 (Fed. Cir. 1983); see also Vas-Cath, Inc. v. Mahurkar, 935 F.2d at1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. See e.g., Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. Union Oil v. Atlantic Richfield Co., 208 F.3d 989, 996 (Fed. Cir. 2000).

The Current Invention is Adequately Described

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains.

The present invention pertains to the field of recombinant DNA/protein technology. It is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made. The subject matter of the pending claims concerns nucleic acids having a specified sequence identity with the disclosed polynucleotide sequence of SEQ ID NO: 119, or encoding a polypeptide with the specified polypeptide sequence of SEQ ID NO: 120, and as amended, with the functional recitation: "wherein said isolated nucleic acid is more highly expressed in esophageal tumor tissue, lung tumor tissue, normal kidney tissue, or normal skin tissue compared to normal esophageal tissue, normal lung tissue, kidney tumor tissue or melanoma tumor tissue, respectively, or wherein said isolated nucleic acid encodes a polypeptide that is more highly expressed in esophageal tumor tissue, lung tumor tissue, normal kidney tissue, or normal skin tissue compared to normal esophageal tissue, normal lung tissue, kidney tumor tissue or melanoma tumor tissue, respectively". Other claims relate to nucleic acids which hybridize to nucleic acids of SEQ ID NO: 119, or polynucleotides which encode a polypeptide of SEQ ID NO: 120, under the specified stringent conditions. Based on the detailed description of

the cloning and expression of variants of PRO1573 in the specification, the description of the gene amplification assay, the actual reduction to practice of sequences SEQ ID NOs: 119 and 120, and the functional recitation in the instant claims, Applicants submit that one of skill in the art would know that Applicants possessed the subject matter of the pending claims. Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

Rejection under 35 U.S.C. §102(b) - Anticipation

The PTO rejects Claims 1-7, 9 and 11-13 as anticipated under 35 U.S.C. § 102(b) by Keen et al. (Accession No: P56748) (hereinafter Keen), which the PTO states was published November, 1999. The PTO states that Keen discloses nucleotides encoding the amino acid sequence of SEQ ID NO: 120 of the instant invention. Applicants respectfully traverse.

To be anticipated under 35 U.S.C. § 102(b), the invention must be patented or described in a printed publication "more than one year prior to the date of the application for patent in the United States." 35 U.S.C. § 102(b). Applicants submit that Keen does not anticipate any of the pending claims because it was not published more than one year prior to the date of the instant application for patent in the United States. The instant application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, with is a continuation-in-part of, and claims priority under 35 U.S.C. § 120 to, US Application 09/403297 filed 10/18/1999, now abandoned, which is the National Stage filed under 35 U.S.C. § 371 of PCT Application PCT/US99/20111 filed 9/1/1999, which claims priority under 35 U.S.C. § 119 to US Provisional Application 60/105002 filed 10/20/1998.

According to the PTO, Keen was published November, 1999. Thus, Keen was not published more than one year prior to the filing of either PCT Application PCT/US00/23328 filed August 24, 2000, or US Provisional Application 60/105002 filed October 20, 1998. The instant application claims priority to both, and therefore Keen cannot be cited as prior art against the instant application under 35 U.S.C. § 102(b). Thus, Applicants respectfully request that the rejection under 35 USC §102(b) be withdrawn.

Rejection under 35 U.S.C. §103(a) – Obviousness

The PTO rejects Claims 14-20 under 35 U.S.C. § 103(a) as unpatentable over Keen et al. in view of Jacobs et al. (U.S. Patent No.: 5,965,397). The PTO asserts that Keen does not teach hybridization of nucleic acid sequences, vector and host cells, but Jacobs does. The PTO concludes that it would have been obvious to one of skill in the art to combine the teaching of Keen with those of Jacobs.

As discussed above in the rejection under 35 U.S.C. § 102(b), Applicants are entitled to priority to U.S. Provisional Application No. 60/105002 filed October 20, 1998. This application includes the disclosure of the full length sequence of SEQ ID NOS: 119 and 120. As the October 20, 1998 date precedes the date of Keen, November, 1999, Applicants have shown possession of the claimed invention prior to Keen.

The well-established "Stempel Doctrine" stands for the proposition that a patent applicant can effectively swear back of and remove a cited prior art reference by showing that he or she made that portion of the claimed invention that is disclosed in the prior art reference. (*In re Stempel*, 113 USPQ 77 (CCPA 1957)). In other words, a patent applicant need not demonstrate that he or she made the entire claimed invention in order to remove a cited prior art reference. He or she need only demonstrate prior possession of that portion of his or her claimed invention that is disclosed in the prior art reference and nothing more.

The Stempel Doctrine was extended to cases where a reference disclosed the claimed compound but failed to disclose a sufficient utility for it in *In re Moore*, 170 USPQ 260 (CCPA 1971). More specifically, the patent applicant (Moore) claimed a specific chemical compound called PFDC. In support of a rejection of the claim under 35 U.S.C. § 102, the Examiner cited a reference which disclosed the claimed PFDC compound, but did not disclose a utility for that compound. Applicant Moore filed a declaration under 37 C.F.R. § 1.131 demonstrating that he had made the PFDC compound before the effective date of the cited prior art reference, even though he had not yet established a utility for that compound. The lower court found the 131 declaration ineffective to swear back of and remove the cited reference, reasoning that since Moore had not established a utility for the PFDC compound prior to the effective date of the cited prior art reference, he had not yet completed his "invention".

On appeal, however, the CCPA reversed the lower court decision and indicated that the 131 declaration filed by Moore was sufficient to remove the cited reference. The CCPA relied on the established Stempel Doctrine to support its decision, stating:

An applicant need <u>not</u> be required to show [in a declaration under 37 C.F.R. § 1.131] any more acts with regard to the subject matter claimed that can be carried out by one of ordinary skill in the pertinent art following the description contained in the reference....the determination of a practical utility when one is not obvious need <u>not</u> have been accomplished prior to the date of a reference unless the reference also teaches how to use the compound it describes. (<u>Id</u>. at 267, emphasis added).

Thus, *In re Moore* confirms the Stempel Doctrine, holding that in order to effectively remove a cited reference with a declaration under 37 C.F.R. § 1.131, an applicant need only show that portion of his or her claimed invention that appears in the cited reference. Moreover, *In re Moore* stands for the proposition that when a cited reference discloses a claimed chemical compound either absent a utility or with a utility that is different from the one appearing in the claims at issue, a patent applicant can effectively swear back of that reference by simply showing prior possession of the claimed chemical compound. In other words, under this scenario, the patent applicant need <u>not</u> demonstrate that he or she had discovered a patentable utility for the claimed chemical compound prior to the effective date of the prior art reference.

While these cases discuss the ability to effectively swear back of the cited reference by way of a 131 declaration, Applicants submit that the same reasoning applies here, where the application claims priority back to a disclosure that predates the cited reference. Keen discloses a sequence which encodes SEQ ID NO: 120, and nothing more. Applicants demonstrated, by means of the disclosure in their provisional application filed October 20, 1998, that they were in possession of so much of the claimed invention, i.e. SEQ ID NO: 120, as disclosed in the Keen reference dated November, 1999. Thus, Applicants respectfully submit that the cited reference is not available as prior art, and request that the rejection under 35 USC §103(a) be withdrawn.

Appl. No. : Filed :

10/063,732 May 8, 2002

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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DELETION OF INVENTORS

Please correct the inventorship under 37 CFR §1.48(b) by removing the following inventors from the present application:

Dan L. Eaton, Ellen Filvaroff, Mary E. Gerritsen, and Colin K. Watanabe.